

ALINIA- nitazoxanide tablet
ALINIA- nitazoxanide powder, for suspension
Romark Laboratories, L.C.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALINIA safely and effectively. See full prescribing information for ALINIA.

ALINIA® (nitazoxanide) tablets, for oral use
ALINIA® (nitazoxanide) for oral suspension

Initial U.S. Approval: 2002

----- **INDICATIONS AND USAGE** -----

ALINIA is an antiprotozoal indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*(1).

Limitations of Use:

ALINIA has not been shown to be effective for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients (1).

----- **DOSAGE AND ADMINISTRATION** -----

- ALINIA Tablets should not be administered to pediatric patient 11 years of age or younger (2.1)
- Dosage for treatment of diarrhea caused by *G. lamblia* or *C. parvum* (2.1):

Age	Dosage	Duration
1-3 years	5 mL of ALINIA for Oral Suspension (100 mg nitazoxanide) every 12 hours with food	3 days
4-11 years	10 mL of ALINIA for Oral Suspension (200 mg nitazoxanide) every 12 hours with food	
12 years and older	One ALINIA Tablet (500 mg nitazoxanide) every 12 hours with food <u>or</u> 25 mL of ALINIA for Oral Suspension (500 mg nitazoxanide) every 12 hours with food	

----- **DOSAGE FORMS AND STRENGTHS** -----

- ALINIA Tablets: 500 mg (3.1)
- ALINIA for Oral Suspension: 100 mg/5 mL (3.2)

----- **CONTRAINDICATIONS** -----

Hypersensitivity (4.1)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions in $\geq 2\%$ of patients were abdominal pain, headache, chromaturia, and nausea (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Romark at 813-282-8544 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

Competition for binding sites may occur when administered concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices. Monitor for adverse reactions (7).

----- **USE IN SPECIFIC POPULATIONS** -----

Pediatric Patients: Safety and efficacy of ALINIA for Oral Suspension in pediatric patients less than one year of age has not been studied (8.4).

Revised: 6/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*:

ALINIA for Oral Suspension (patients 1 year of age and older) and ALINIA Tablets (patients 12 years and older) are indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum*.

Limitations of Use

ALINIA for Oral Suspension and ALINIA Tablets have not been shown to be effective for the treatment of diarrhea caused by *Cryptosporidium parvum* in HIV-infected or immunodeficient patients [see *Clinical Studies (14.2)*]

2 DOSAGE & ADMINISTRATION

2.1 Recommended Dosage and Important Administration Instructions

Important Administration Instructions for Pediatric Patients 11 years of Age or Younger:

ALINIA tablets should not be administered to pediatric patients 11 years of age or younger because a single tablet contains a greater amount of nitazoxanide than the recommended dosing in this pediatric age group.

Table 1. Recommended Dosage

Age	Dosage	Duration
1-3 years	5 mL of ALINIA for Oral suspension (100 mg nitazoxanide) taken orally every 12 hours with food	3 Days
4-11 years	10 mL of ALINIA for Oral Suspension (200 mg nitazoxanide) taken orally every 12 hours with food	
12 years and older	One ALINIA Tablet (500 mg nitazoxanide) taken orally every 12 hours with food <u>or</u> 25 mL of ALINIA for Oral Suspension (500 mg nitazoxanide) taken orally every 12 hours with food	

2.2 Directions for Mixing ALINIA for Oral Suspension

Reconstitute ALINIA for Oral Suspension as follows:

- Measure 48 mL of water for preparation of the 100 mg/5 mL suspension
- Tap bottle until all powder flows freely.
- Add approximately one-half of the 48 mL of water required for reconstitution and shake vigorously to suspend powder.
- Add remainder of water and again shake vigorously

Keep container tightly closed, and shake the suspension well before each administration. The reconstituted suspension may be stored for 7 days at room temperature, after which any unused portion must be discarded.

3 DOSAGE FORMS AND STRENGTHS

3.1 ALINIA Tablets (500 mg)

Round, yellow, film-coated tablets debossed with ALINIA on one side and 500 on the other side. Each tablet contains 500 mg of nitazoxanide.

3.2 ALINIA for Oral Suspension (100 mg/5 mL)

Pink-colored powder formulation that, when reconstituted as directed, contains 100 mg nitazoxanide/5 mL. The reconstituted suspension has a pink color and strawberry flavor.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

ALINIA Tablets and ALINIA for Oral Suspension are contraindicated in patients with a prior hypersensitivity to nitazoxanide or any other ingredient in the formulations.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of ALINIA was evaluated in 2177 HIV-uninfected subjects 12 months of age and older who received ALINIA Tablets or ALINIA for Oral Suspension at the recommended dose for at least three days. In pooled controlled clinical trials involving 536 HIV-uninfected subjects treated with ALINIA Tablets or ALINIA for Oral Suspension, the most common adverse reactions were abdominal pain, headache, chromaturia and nausea ($\geq 2\%$).

Safety data were analyzed separately for 280 HIV-uninfected subjects ≥ 12 years of age receiving ALINIA at the recommended dose for at least three days in 5 placebo-controlled clinical trials and for 256 HIV-uninfected subjects 1 through 11 years of age in 7 controlled clinical trials. There were no differences between the adverse reactions reported for ALINIA-treated subjects based upon age.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ALINIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following is a list of adverse reactions spontaneously reported with ALINIA Tablets which were not included in clinical trial listings:

Gastrointestinal disorders: diarrhea, gastroesophageal reflux disease

Nervous System disorders: dizziness

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: rash, urticaria

7 DRUG INTERACTIONS

7.1 Highly Protein Bound Drugs with Narrow Therapeutic Indices

Tizoxanide (the active metabolite of nitazoxanide) is highly bound to plasma protein ($>99.9\%$). Therefore, monitor for adverse reactions when administering nitazoxanide concurrently with other highly plasma protein-bound drugs with narrow therapeutic indices, as competition for binding sites may occur (e.g., warfarin).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with ALINIA in pregnant women to inform a drug-associated risk. No teratogenicity or fetotoxicity was observed in animal reproduction studies with administration of nitazoxanide to pregnant rats and rabbits during organogenesis at exposure 30 and 2 times, respectively, the exposure at the maximum recommended human dose of 500 mg twice daily based on body surface area (BSA).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Nitazoxanide was administered orally to pregnant rats at doses of 0, 200, 800 or 3200 mg/kg/day on gestation days 6 to 15. Nitazoxanide produced no evidence of systemic maternal toxicity when

administer once daily via oral gavage to pregnant female rats at levels up to 3200 mg/kg/day during the period of organogenesis .

In rabbits, nitazoxanide was administered at doses of 0, 25, 50, or 100 mg/kg/day on gestation days 7 to 20. Oral treatment of pregnant rabbits with nitazoxanide during organogenesis resulted in minimal maternal toxicity and no external fetal anomalies.

8.2 Lactation

Risk Summary

No information regarding the presence of nitazoxanide in human milk, the effects on the breastfed infant, or the effects on milk production is available. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ALINIA and any potential adverse effects on the breastfed infant from ALINIA or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of ALINIA for Oral Suspension for the treatment of diarrhea caused by *G. lamblia* or *C. parvum* in pediatric patients 1 to 11 years of age has been established based on three (3) randomized, controlled studies with 104 pediatric subjects treated with ALINIA for Oral Suspension 100 mg/5 mL. Furthermore, the safety and efficacy of ALINIA for Oral Suspension for the treatment of diarrhea caused by *G. lamblia* or *C. parvum* in pediatric patients 12 to 17 years of age has been established based on two (2) randomized controlled studies with 44 pediatric subjects treated with ALINIA for Oral Suspension 100 mg/5 mL. [see *Clinical Studies* (14.1)]

The safety and efficacy of ALINIA Tablets for the treatment of diarrhea caused by *G. lamblia* or *C. parvum* in pediatric patients 12 to 17 years of age has been established based on three (3) randomized controlled studies with 47 pediatric subjects treated with ALINIA Tablets 500 mg.

A single ALINIA Tablet contains a greater amount of nitazoxanide than is recommended for use in pediatric patients 11 years or younger. [see *Dosage and Administration* (2.1)].

Safety and efficacy of ALINIA for Oral Suspension in pediatric patients less than one year of age has not been studied.

8.5 Geriatric Use

Clinical studies of ALINIA Tablets and ALINIA for Oral Suspension did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing ALINIA Tablets and ALINIA for Oral Suspension.

8.6 Renal and Hepatic Impairment

The pharmacokinetics of nitazoxanide in patients with compromised renal or hepatic function has not been studied.

8.7 HIV-Infected or Immunodeficient Patients

ALINIA Tablets and ALINIA for Oral Suspension have not been studied for the treatment of diarrhea caused by *G. lamblia* in HIV-infected or immunodeficient patients. ALINIA Tablets and ALINIA for Oral Suspension have not been shown to be superior to placebo for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients [see *Clinical Studies* (14)]

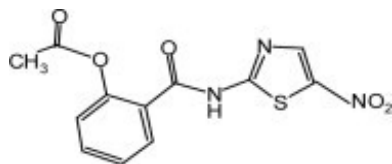
10 OVERDOSAGE

Limited information on nitazoxanide overdosage is available. Single oral doses of up to 4000 mg

nitazoxanide have been administered to healthy adult volunteers without significant adverse effects. In the event of overdose, gastric lavage may be appropriate soon after oral administration. Patients should be observed and given symptomatic and supportive treatment. There is no specific antidote for overdose with ALINIA. Because nitazoxanide is highly protein bound (>99.9%), dialysis is unlikely to significantly reduce plasma concentrations of the drug.

11 DESCRIPTION

ALINIA Tablets and ALINIA for Oral Suspension contain the active ingredient, nitazoxanide, a synthetic antiprotozoal for oral administration. Nitazoxanide is a light yellow crystalline powder. It is poorly soluble in ethanol and practically insoluble in water. Chemically, nitazoxanide is 2-acetyloxy- *N*-(5-nitro-2-thiazolyl)benzamide. The molecular formula is C₁₂H₉N₃O₅S and the molecular weight is 307.3. The structural formula is:



ALINIA Tablets contain 500 mg of nitazoxanide and the following inactive ingredients: maize starch, pregelatinized corn starch, hydroxypropyl methylcellulose, sucrose, sodium starch glycolate, talc, magnesium stearate, soy lecithin, polyvinyl alcohol, xanthan gum, titanium dioxide, D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake.

ALINIA for Oral Suspension, when reconstituted with 48 mL of water, produces 60 mL of a homogeneous suspension with a pink color that contains 100 mg nitazoxanide per 5 mL and the following inactive ingredients: sodium benzoate, sucrose, xanthan gum, microcrystalline cellulose and carboxymethylcellulose sodium, anhydrous citric acid, sodium citrate dihydrate, maltodextrin, modified food starch, triacetin, FD&C Red No. 40 and artificial strawberry flavoring.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitazoxanide is an antiprotozoal [*see Microbiology (12.4)*].

12.3 Pharmacokinetics

Absorption

Single Dosing:

Following oral administration of ALINIA Tablets or Oral Suspension, the parent drug, nitazoxanide, is not detected in plasma. The pharmacokinetic parameters of the metabolites, tizoxanide and tizoxanide glucuronide are shown in Tables 2 and 3 below.

Table 2. Mean (+/- SD) plasma pharmacokinetic parameters of tizoxanide and tizoxanide glucuronide following administration of a single dose of one 500 mg ALINIA Tablet with food to subjects ≥12 years of age

Age	Tizoxanide			Tizoxanide Glucuronide		
	C _{max} (µg/mL)	T _{max} (hr)	AUC _t (µg•hr/mL)	C _{max} (µg/mL)	T _{max} (hr)	AUC _t (µg•hr/mL)
12 - 17	0.1 (0.1)	4.0 (1.4)	20.5 (24.2)	7.2 (1.0)	4.0 (2.8)	46.5 (18.2)

years	9.1 (0.1)	4.0 (1-4)	39.5 (24.2)	7.5 (1.9)	4.0 (2-6)	40.5 (10.2)
>18 years	10.6 (2.0)	3.0 (2-4)	41.9 (6.0)	10.5 (1.4)	4.5 (4-6)	63.0 (12.3)

*T_{max} is given as a Mean (Range)

Table 3. Mean (+/-SD) plasma pharmacokinetic of tizoxanide and tizoxanide glucuronide parameter values following administration of single dose of ALINIA for Oral Suspension with food to subjects ≥1year of age

Age	Dose	Tizoxanide			Tizoxanide Glucuronide		
		C _{max} (µg/mL)	*T _{max} (hr)	AUC _t (µg•hr/mL)	C _{max} (µg/mL)	*T _{max} (hr)	AUC _{inf} (µg•hr/mL)
1-3 years	100 mg	3.11 (2.0)	3.5 (2-4)	11.7 (4.46)	3.64 (1.16)	4.0 (3-4)	19.0 (5.03)
4-11 years	200 mg	3.00 (0.99)	2.0 (1-4)	13.5 (3.3)	2.84 (0.97)	4.0 (2-4)	16.9 (5.00)
>18 years	500 mg	5.49 (2.06)	2.5 (1-5)	30.2 (12.3)	3.21 (1.05)	4.0 (2.5-6)	22.8 (6.49)

*T_{max} is given as a Mean (Range)

Multiple dosing:

Following oral administration of a single ALINIA Tablet every 12 hours for 7 consecutive days, there was no significant accumulation of nitazoxanide metabolites tizoxanide or tizoxanide glucuronide detected in plasma.

Bioavailability:

ALINIA for Oral Suspension is not bioequivalent to ALINIA Tablets. The relative bioavailability of the suspension compared to the tablet was 70%.

When ALINIA Tablets are administered with food, the AUC_t of tizoxanide and tizoxanide glucuronide in plasma is increased almost two-fold and the C_{max} is increased by almost 50%.

When ALINIA for Oral Suspension was administered with food, the AUC_t of tizoxanide and tizoxanide glucuronide increased by about 45-50% and the C_{max} increased by ≤10%.

ALINIA Tablets and ALINIA for Oral Suspension were administered with food in clinical trials and hence they are recommended to be administered with food [see Dosage and Administration (2.1)]

Distribution

In plasma, more than 99% of tizoxanide is bound to proteins.

Elimination

Metabolism

Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation.

Excretion

Tizoxanide is excreted in the urine, bile and feces, and tizoxanide glucuronide is excreted in urine and bile. Approximately two-thirds of the oral dose of nitazoxanide is excreted in the feces and one-third in the urine.

Specific Populations

Pediatric Patients

The pharmacokinetics of tizoxanide and tizoxanide glucuronide following administration of ALINIA Tablets in pediatric patients 12-17 years of age are provided above in Table 2. The pharmacokinetics of tizoxanide and tizoxanide glucuronide following administration of ALINIA for Oral Suspension in pediatric patients 1-11 years of age are provided above in Table 3.

Drug Interaction Studies

In vitro studies have demonstrated that tizoxanide has no significant inhibitory effect on cytochrome P450 enzymes.

12.4 MICROBIOLOGY

Mechanism of Action

The antiprotozoal activity of nitazoxanide is believed to be due to interference with the pyruvate:ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction which is essential to anaerobic energy metabolism. Studies have shown that the PFOR enzyme from *G. lamblia* directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of *C. parvum* appears to be similar to that of *G. lamblia*. Interference with the PFOR enzyme-dependent electron transfer reaction may not be the only pathway by which nitazoxanide exhibits antiprotozoal activity.

Resistance

A potential for development of resistance by *C. parvum* or *G. lamblia* to nitazoxanide has not been examined.

Antimicrobial Activity

Nitazoxanide and its metabolite, tizoxanide, are active *in vitro* in inhibiting the growth of (i) sporozoites and oocysts of *C. parvum* and (ii) trophozoites of *G. lamblia*.

Susceptibility Test Methods

For protozoa such as *C. parvum* and *G. lamblia*, standardized tests for use in clinical microbiology laboratories are not available.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies have not been conducted.

Mutagenesis

Nitazoxanide was not genotoxic in the Chinese hamster ovary (CHO) cell chromosomal aberration assay or the mouse micronucleus assay. Nitazoxanide was genotoxic in one tester strain (TA100) in the Ames bacterial mutation assay.

Impairment of Fertility

Nitazoxanide did not adversely affect male or female fertility in the rat at 2400 mg/kg/day (approximately 20 times the clinical adult dose adjusted for body surface area).

14 CLINICAL STUDIES

14.1 Diarrhea Caused by *G. lamblia*

Diarrhea caused by *G. lamblia* in adults and adolescents 12 years of age or older:

In a double-blind, controlled trial (Study 1) conducted in Peru and Egypt in adults and adolescents with diarrhea and with one or more enteric symptoms (e.g., abdominal pain, nausea, vomiting, fever, abdominal distention, loss of appetite, flatulence) caused by *G. lamblia*, a three-day course of treatment with ALINIA Tablets administered 500 mg BID was compared with a placebo tablet for 3 days. A third group of patients received open-label ALINIA for Oral Suspension administered 500 mg/25 mL of suspension BID for 3 days. A second double-blind, controlled trial (Study 2) conducted in Egypt in adults and adolescents with diarrhea and with or without enteric symptoms (e.g., abdominal colic, abdominal tenderness, abdominal cramps, abdominal distention, fever, bloody stool) caused by *G. lamblia* compared ALINIA Tablets administered 500 mg BID for 3 days to a placebo tablet. For both of these studies, clinical response was evaluated 4 to 7 days following the end of treatment. A clinical response of ‘well’ was defined as ‘no symptoms, no watery stools and no more than 2 soft stools with no hematochezia within the past 24 hours’ or ‘no symptoms and no unformed stools within the past 48 hours.’ The following clinical response rates were obtained:

Table 4. Adult and Adolescent Patients with Diarrhea Caused by *G. lamblia*

Clinical Response Rates* 4 to 7 Days Post-therapy

% (Number of Successes/Total)

	ALINIA Tablets	ALINIA for Oral Suspension	Placebo Tablets
Study 1	85% (46/54) ¶ §	83% (45/54) ¶ §	44% (12/27)
Study 2	100% (8/8)	-	30% (3/10)

* Includes all patients randomized with *G. lamblia* as the sole pathogen. Patients failing to complete the studies were treated as failures.

¶ Clinical response rates statistically significantly higher when compared to placebo.

§ The 95% confidence interval of the difference in response rates for the tablet and suspension is (-14%, 17%).

Some patients with ‘well’ clinical responses had *G. lamblia* cysts in their stool samples 4 to 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based upon clinical response to treatment.

Diarrhea caused by *G. lamblia* in pediatric patients 1 through 11 years of age:

In a randomized, controlled trial conducted in Peru in 110 pediatric patients with diarrhea and with or without enteric symptoms (e.g., abdominal distention, right iliac fossa tenderness) caused by *G. lamblia*, a three-day course of treatment with nitazoxanide (100 mg BID in pediatric patients ages 24-47 months, 200 mg BID in pediatric patients ages 4 through 11 years) was compared to a five-day course of treatment with metronidazole (125 mg BID in pediatric patients ages 2 through 5 years, 250 mg BID in pediatric patients ages 6 through 11 years). Clinical response was evaluated 7 to 10 days following initiation of treatment with a ‘well’ response defined as ‘no symptoms, no watery stools and no more than 2 soft stools with no hematochezia within the past 24 hours’ or ‘no symptoms and no unformed stools within the past 48 hours.’ The following clinical cure rates were obtained:

Table 5. Clinical Response Rates in Pediatric Patients 7 to 10 Days Following Initiation of Therapy

Intent-to-Treat and Per Protocol Analyses

% (Number of Successes/Total), [95% Confidence Interval]

Population	Nitazoxanide (3 days)	Metronidazole (5 days)	95% CI Diff [§]
Intent-to-treat analysis [†]	85% (47/55)	80% (44/55)	[-9%, 20%]
Per protocol analysis [¶]	90% (43/48)	83% (39/47)	[-8%, 21%]

[†] Intent-to-treat analysis includes all patients randomized with patients not completing the study treated as failures.

[¶] Per protocol analysis includes only patients who took all of their medication and completed the study. Seven patients in each treatment group missed at least one dose of medication and one in the metronidazole treatment group was lost to follow-up.

[§] 95% Confidence Interval on the difference in response rates (nitazoxanide-metronidazole).

Some patients with ‘well’ clinical responses had *G. lamblia* cysts in their stool samples 4 to 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based upon clinical response to treatment.

14.2 Diarrhea Caused by *C. parvum*

Diarrhea caused by *C. parvum* in adults and adolescents 12 years of age or older:

In a double-blind, controlled trial conducted in Egypt in adults and adolescents with diarrhea and with or without enteric symptoms (e.g., abdominal pain/cramps, nausea, vomiting) caused by *C. parvum*, a three-day course of treatment with ALINIA Tablets administered 500 mg BID was compared with a placebo tablet for 3 days. A third group of patients received open-label ALINIA for Oral Suspension administered 500 mg/25 mL of suspension BID for 3 days. Clinical response was evaluated 4 to 7 days following the end of treatment. A clinical response of ‘well’ was defined as ‘no symptoms, no watery stools and no more than 2 soft stools within the past 24 hours’ or ‘no symptoms and no unformed stools within the past 48 hours.’ The following clinical response rates were obtained:

**Table 6. Clinical Response Rates in Adult and Adolescent Patients 4 to 7 Days Post-therapy
% (Number of Successes/Total)**

	ALINIA Tablets	ALINIA Suspension	Placebo Tablets
Intent-to-treat analysis*	96% (27/28) [¶] [§]	87% (27/31) [¶] [§]	41% (11/27)

* Includes all patients randomized with *C. parvum* as the sole pathogen. Patients failing to complete the study were treated as failures.

[¶] Clinical response rates statistically significantly higher when compared to placebo.

[§] The 95% confidence interval of the difference in response rates for the tablet and suspension is (-10%, 28%).

In a second double-blind, placebo-controlled study of nitazoxanide tablets conducted in Egypt in adults and adolescents with diarrhea and with or without enteric symptoms (e.g., abdominal colic, abdominal cramps, epigastric pain) caused by *C. parvum* as the sole pathogen, clinical and parasitological response rates showed a similar trend to the first study. Clinical response rates, evaluated 2 to 6 days following the end of treatment, were 71% (15/21) in the nitazoxanide group and 42.9% (9/21) in the placebo group.

Some patients with ‘well’ clinical responses had *C. parvum* oocysts in their stool samples 4 to 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based upon clinical response to treatment.

Diarrhea caused by *C. parvum* in pediatric patients 1 through 11 years of age :

In two double-blind, controlled trials in pediatric patients with diarrhea and with or without enteric symptoms (e.g., abdominal distention, colic, left iliac fossa tenderness) caused by *C. parvum*, a three-

day course of treatment with nitazoxanide (100 mg BID in pediatric patients ages 12-47 months, 200 mg BID in pediatric patients ages 4 through 11 years) was compared with a placebo. One study was conducted in Egypt in outpatients ages 1 through 11 years with diarrhea caused by *C. parvum*. Another study was conducted in Zambia in malnourished pediatric patients admitted to the hospital with diarrhea caused by *C. parvum*. Clinical response was evaluated 3 to 7 days post-therapy with a ‘well’ response defined as ‘no symptoms, no watery stools and no more than 2 soft stools within the past 24 hours’ or ‘no symptoms and no unformed stools within the past 48 hours.’ The following clinical response rates were obtained:

Table 7. Clinical Response Rates in Pediatric Patients 3 to 7 Days Post-therapy Intent-to-Treat Analyses

% (Number of Successes/Total)

Population	Nitazoxanide*	Placebo
Outpatient Study, age 1 - 11 years	88% (21/24)	38% (9/24)
Inpatient Study, Malnourished ¶, age 12-35 months	56% (14/25)	23% (5/22)

* Clinical response rates statistically significantly higher compared to placebo.

¶ 60% considered severely underweight, 19% moderately underweight, 17% mild underweight.

Some patients with ‘well’ clinical responses had *C. parvum* oocysts in their stool samples 3 to 7 days following the end of treatment. The relevance of stool examination results in these patients is unknown. Patients should be managed based upon clinical response to treatment.

Diarrhea caused by *C. parvum* in Acquired Immune Deficiency Syndrome (AIDS) patients :

A double-blind, placebo-controlled trial did not produce clinical cure rates that were significantly different from the placebo control when conducted in hospitalized, severely malnourished pediatric patients with acquired immune deficiency syndrome (AIDS) in Zambia. In this study, the pediatric patients received a three day course of nitazoxanide suspension (100 mg BID in pediatric patients ages 12-47 months, 200 mg BID in pediatric patients ages 4 through 11 years) and were evaluated for response four days after the end of treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 ALINIA Tablets (500 mg)

ALINIA tablets are round, yellow, film-coated tablets debossed with ALINIA on one side and 500 on the other side. Each tablet contains 500 mg of nitazoxanide. The tablets are packaged in HDPE bottles of 12 and 30 tablets.

Bottles of 12 tablets NDC 67546-111-14

Bottles of 30 tablets NDC 67546-111-12

Store the tablets at 25 °C (77 °F); excursions permitted to 15 °C-30 °C (59 °F-86 °F). [See USP Controlled Room Temperature]

16.2 ALINIA for Oral Suspension (100 mg/5 mL)

ALINIA for oral suspension is a pink-colored powder formulation that, when reconstituted as directed, contains 100 mg nitazoxanide/5 mL. The reconstituted suspension has a pink color and strawberry flavor. Alinia for oral suspension is available as:

Bottles of 60 mL NDC 67546-212-21

Store the unsuspended powder at 25 °C (77 °F); excursions permitted to 15 °C-30 °C (59 °F-86 °F).

[See USP Controlled Room Temperature]

The reconstituted suspension may be stored for 7 days at room temperature, after which any unused portion must be discarded [see *Dosage and Administration* (2.2)]

17 PATIENT COUNSELING INFORMATION

Advise patients and parents/caregivers of pediatric patients taking ALINIA Tablets or ALINIA for Oral Suspension of the following information:

Dosage and Administration:

ALINIA Tablets and ALINIA for Oral Suspension should be taken with food.

ALINIA for Oral Suspension: The container should be kept tightly closed, and the suspension should be shaken well before each administration. The suspension may be stored at room temperature for 7 days, after which any unused portion must be discarded.

Drug-drug Interactions:

Avoid concurrent warfarin use.

MANUFACTURER INFORMATION



Romark, L.C.
3000 Bayport Drive, Suite 200, Tampa, FL 33607
Telephone: 813-282-8544, Fax: 813-282-1162
E-mail: customer.service@romark.com
Web site: www.romark.com

ALINIA is a registered trademark of Romark.

PI-111/212-06 R.06/19

Alinia (nitazoxanide) Tablets - 30 ct Label

NDC 67546-111-12

Alinia®

(nitazoxanide) tablets

500 mg

Rx Only 30 TABLETS

NDC 67546-111-12
FPO NDC/UPC
3 67546 11112 7

Lot#:

Exp:



STORAGE AND STABILITY:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]

DOSE AND ADMINISTRATION:
Age ≥ 12 years: one tablet (500 mg nitazoxanide) every 12 hours for 3 days, with food. Please see accompanying prescribing information.

This bottle contains 30 tablets. Each tablet contains 500 mg nitazoxanide.

Manufactured for:
Romark, L.L.C.
3000 Bayport Drive, Suite 200,
Tampa, FL 33607

ROMARK

BL-111-12.01 R04/17

Alinia (nitazoxanide) Tablets - 30 ct Carton

NDC 67546-111-12

Alinia (nitazoxanide) tablets

500 mg

Rx Only 30 TABLETS



Alinia (nitazoxanide) Tablets - 2 ct Sample Label

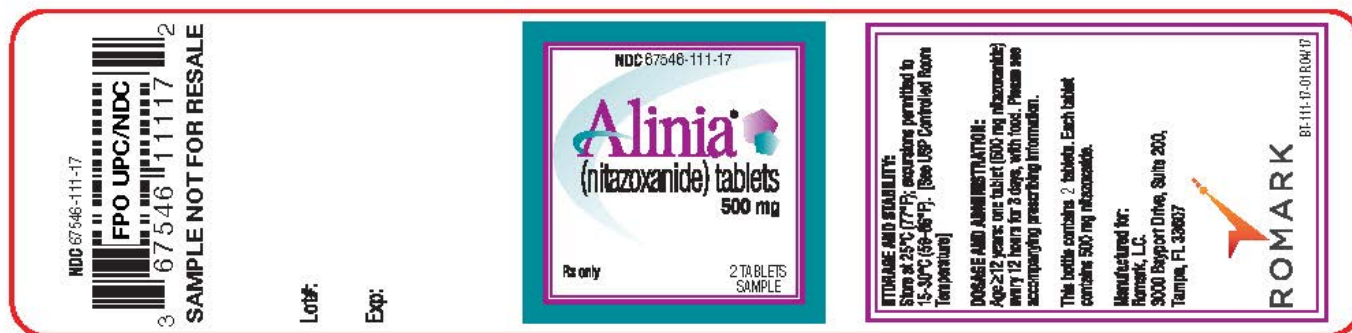
NDC 67546-111-17

Alinia®

(nitazoxanide) tablets

500 mg

Rx only 2 TABLETS SAMPLE



Alinia (nitazoxanide) Tablets - 2 ct Sample Carton

NDC 67546-111-17

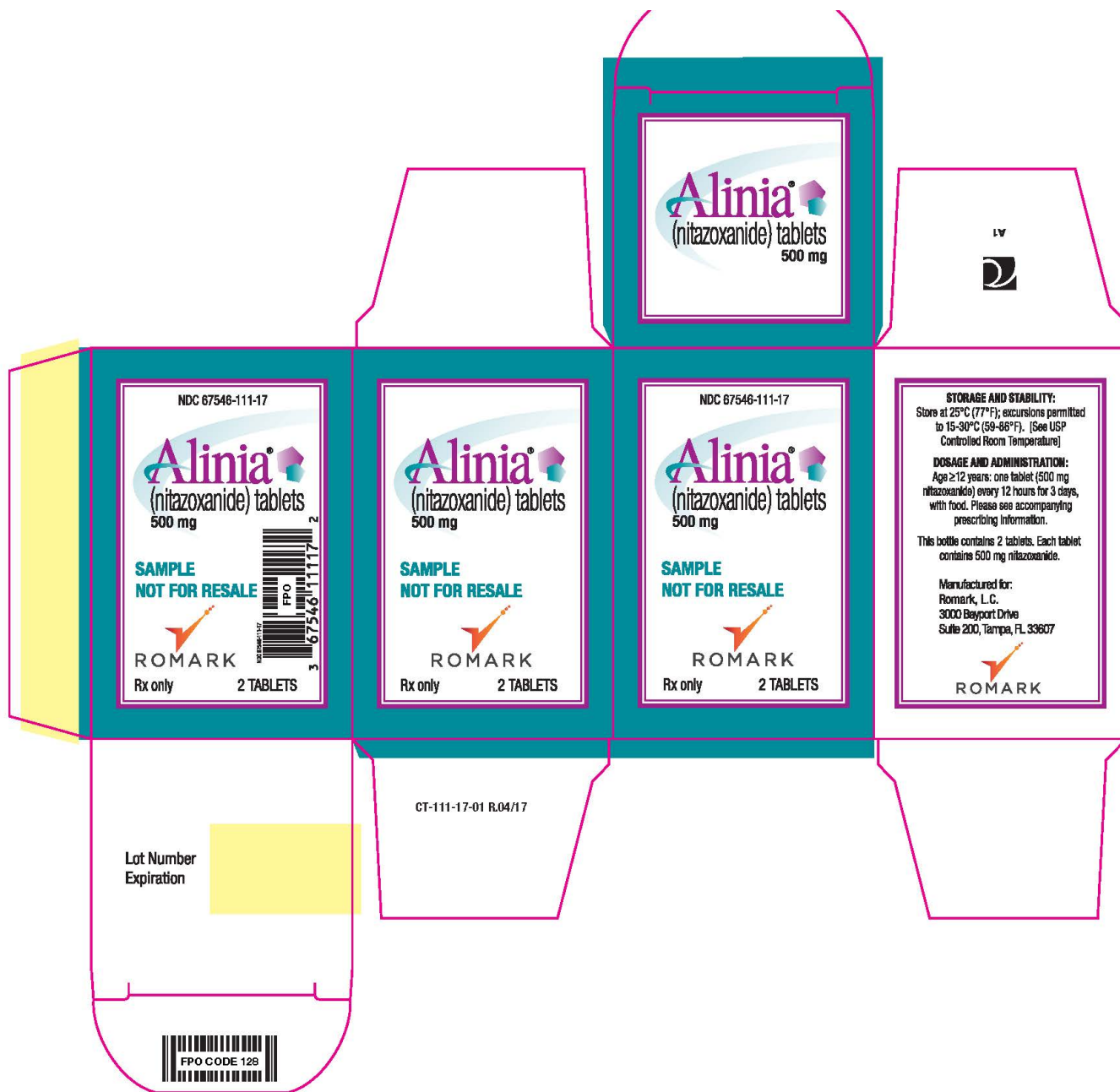
Alinia (nitazoxanide) tablets

500 mg

SAMPLE NOT FOR RESALE

Romark logo

Rx Only 2 TABLETS



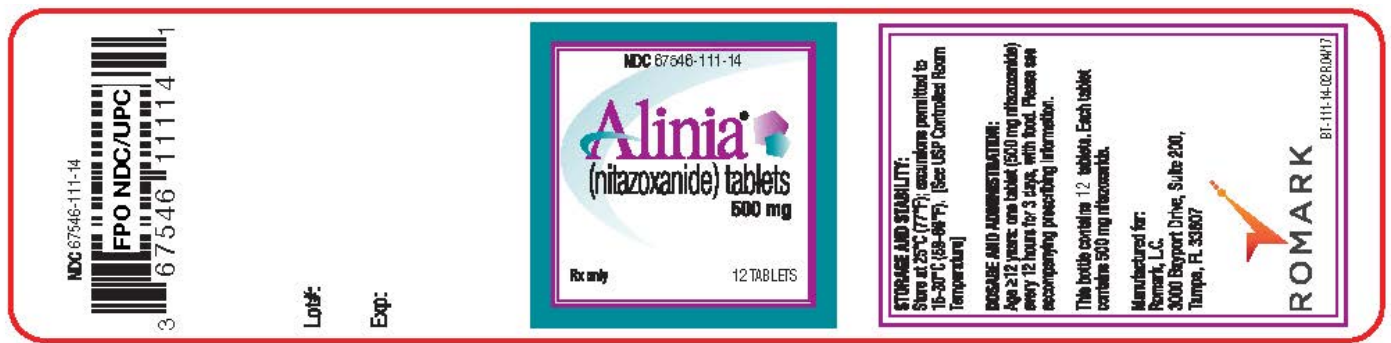
Alinia (nitazoxanide) Tablets - 12 ct Label

NDC 67546-111-14

Alinia® (nitazoxinide) tablets

500 mg

Rx only 12 TABLETS



Alinia (nitazoxanide) Tablets - 12 ct Carton

NDC 67546-111-14

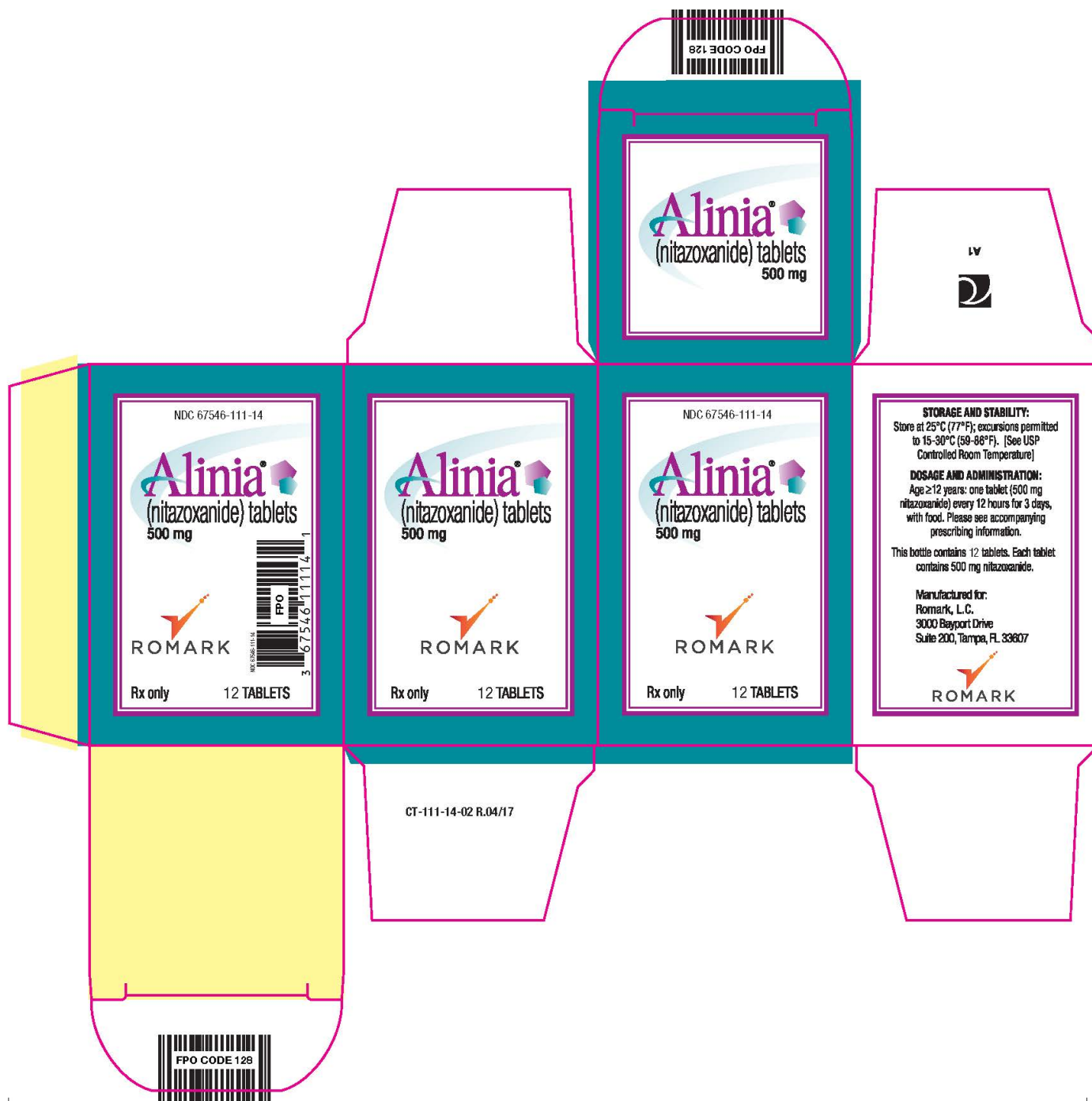
Alinia®

(nitazoxanide) tablets

500 mg

Romark Logo

Rx only 12 TABLETS



Alinia (nitazoxanide) for Oral Suspension - 60 mL Container Label

NDC 67546-212-21

Alinia (nitazoxanide) for Oral Suspension 100 mg/5 mL

Reconstitute with 48 mL water

SHAKE WELL BEFORE USING

Any unused portion must be discarded 7 days after mixing

60 mL reconstituted

Rx only

NDC 67546-212-21



LOT #:

EXP. DATE:

60 mL
reconstituted

Rx only



NDC 67546-212-21

Alinia
(nitazoxanide)

for Oral Suspension
100 mg/5 mL

Reconstitute with 48 mL water
SHAKE WELL BEFORE USING
Any unused portion must be
discarded 7 days after mixing

Storage and Use: Store the unsuspended powder and the reconstituted oral suspension at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). (See USP Controlled Room Temperature) Use within 7 days after mixing. Keep bottle tightly closed. Shake well before each use.

Usual Dosage: Children age 12-47 months, take 5 mL (100 mg nitazoxanide) every 12 hours for 3 days. Children age 4 through 11 years, take 10 mL (200 mg nitazoxanide) every 12 hours for 3 days. Suspension should be taken with food. See accompanying prescribing information.

Directions for Reconstitution: Reconstitute with 48 mL of water. Tap bottle until all powder flows freely. Add approximately one-half of the total amount of water required for reconstitution and shake vigorously to suspend powder. Add remainder of water and again shake vigorously. This provides 60 mL of suspension.

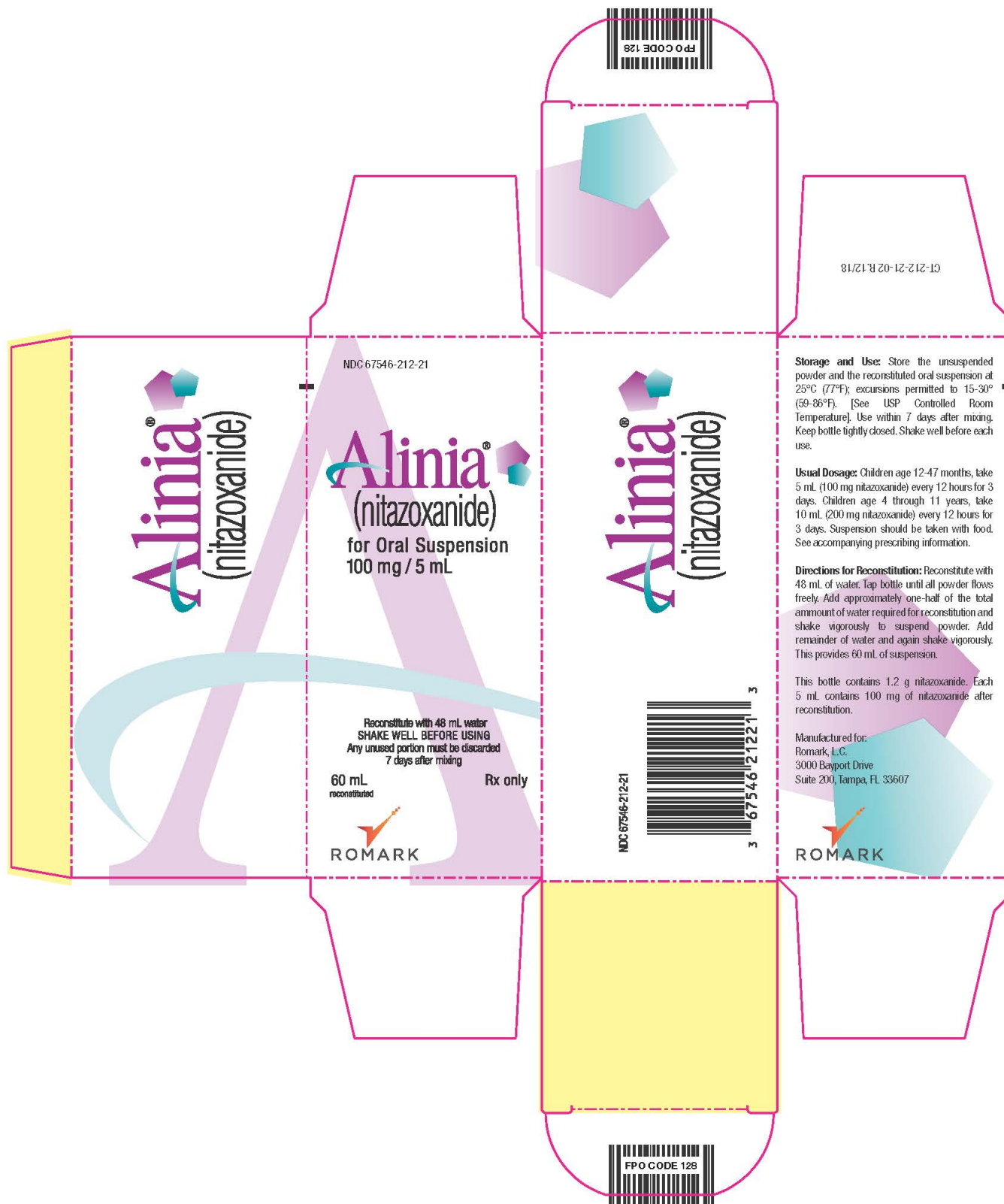
This bottle contains 1.2 g nitazoxanide. Each 5 mL contains 100 mg of nitazoxanide after reconstitution.

Manufactured for:
Romark, L.C.

BT-212-21-01 R.04/17

3000 Bayport Drive, Suite 200, Tampa, FL 33607

Alinia (nitazoxanide) for Oral Suspension - 60 mL Carton



NDC 67546-212-21

Alinia (nitazoxanide) for Oral Suspension 100 mg/5 mL

Reconstitute with 48 mL water

SHAKE WELL BEFORE USING

Any unused portion must be discarded 7 days after mixing

60 mL

Rx only

ALINIA				
nitazoxanide tablet				
Product Information				
Product Type		HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:67546-111
Route of Administration		ORAL		
Active Ingredient/Active Moiety				
Ingredient Name			Basis of Strength	Strength
NITAZO XANIDE (UNII: SOA12P041N) (NITAZOXANIDE - UNII:SOA12P041N)			NITAZOXANIDE	500 mg
Inactive Ingredients				
Ingredient Name				Strength
TITANIUM DIO XIDE (UNII: 15FIX9V2JP)				
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)				
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)				
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)				
STARCH, CORN (UNII: O8232NY3SJ)				
HYPROMELLOSES (UNII: 3NXW29V3WO)				
SUCROSE (UNII: C151H8M554)				
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)				
TALC (UNII: 7SEV7J4R1U)				
MAGNESIUM STEARATE (UNII: 70097M6I30)				
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)				
POLYVINYL ALCOHOL (UNII: 532B59J990)				
XANTHAN GUM (UNII: TTV12P4NEE)				
Product Characteristics				
Color	yellow (yellow)	Score	no score	
Shape	ROUND (ROUND)	Size	13mm	
Flavor		Imprint Code	ALINIA;500	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67546-111-12	1 in 1 CARTON	07/21/2004	
1		30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:67546-111-14	1 in 1 CARTON	07/21/2004	
		12 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination		

2	12 mL BOTTLE, PLASTIC; Type 0: Not a Combination Product		
Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021497	07/21/2004	

ALINIA				
nitazoxanide powder, for suspension				
Product Information				
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:67546-212	
Route of Administration	ORAL			
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
NITAZO XANIDE (UNII: SOA12P041N) (NITAZO XANIDE - UNII:SOA12P041N)		NITAZO XANIDE	100 mg in 5 mL	
Inactive Ingredients				
Ingredient Name			Strength	
XANTHAN GUM (UNII: TTV12P4NEE)				
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)				
CARBOXYMETHYLCELLULOSE SODIUM (UNII: K679OBS311)				
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)				
MALTO DEXTRIN (UNII: 7CVR7L4A2D)				
MODIFIED CORN STARCH (1-OCTENYL SUCCINIC ANHYDRIDE) (UNII: 461P5CJN6T)				
TRIACETIN (UNII: XHX3C3X673)				
FD&C RED NO. 40 (UNII: WZB9127XOA)				
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)				
SUCROSE (UNII: C151H8M554)				
SODIUM BENZOATE (UNII: OJ245FE5EU)				
Product Characteristics				
Color		Score		
Shape		Size		
Flavor	STRAWBERRY (Strawberry)	Imprint Code		
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
	NDC:67546-212			

1	NDC 67546-212-21	1 in 1 CARTON	11/22/2002	
1		60 mL in 1 BOTTLE, GLASS; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
NDA	NDA021498		11/22/2002	

Labeler - Romark Laboratories, L.C. (877685123)

Establishment			
Name	Address	ID/FEI	Business Operations
Catalent Pharma Solutions, LLC		014167995	analysis(67546-212, 67546-111)

Establishment			
Name	Address	ID/FEI	Business Operations
Neolpharma, Inc.		078709787	manufacture(67546-111, 67546-212)

Establishment			
Name	Address	ID/FEI	Business Operations
Romark Global Pharma, LLC		080015267	analysis(67546-111, 67546-212)

Establishment			
Name	Address	ID/FEI	Business Operations
Romark Global Pharma, LLC		117034720	manufacture(67546-111, 67546-212)

Establishment			
Name	Address	ID/FEI	Business Operations
Aphena Pharma Solutions - Tennessee, LLC		128385585	pack(67546-111) , label(67546-111) , relabel(67546-212)

Establishment			
Name	Address	ID/FEI	Business Operations
Whitehouse Analytical Laboratories, LLC		138628008	analysis(67546-111)

Establishment			
Name	Address	ID/FEI	Business Operations
Patheon Puerto Rico, Inc.		143814544	manufacture(67546-212) , analysis(67546-212, 67546-111) , pack(67546-212) , label(67546-212)

Establishment			
Name	Address	ID/FEI	Business Operations
PACE Analytical Inc.		362250102	analysis(67546-111, 67546-212)

Establishment			
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Name	Address	ID/FEI	Business Operations
Romark Belgium, BVBA		370420271	api manufacture(67546-212, 67546-111)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Pharma Solutions, LLC		825745131	manufacture(67546-111)

Establishment

Name	Address	ID/FEI	Business Operations
Catalent Pharma Solutions, LLC		829672745	manufacture(67546-111, 67546-212)

Establishment

Name	Address	ID/FEI	Business Operations
A+ Secure Packaging, LLC		963589036	relabel(67546-212)

Revised: 1/2021

Romark Laboratories, L.C.